Re: DNA Repair, Dysplastic Nevi, and Sunlight Sensitivity in the Development of Cutaneous Malignant Melanoma

Landi et al. *(1)* recently reported in the Journal that DNA repair capacity (DRC) may modify the risk of melanoma in the presence of other strong risk factors, i.e., low tanning ability and/or presence of dysplastic nevi. This study provides the first report that low DRC may be associated with an increased risk for melanoma. Intriguingly, in this study, low DRC does not appear to be a risk factor for melanoma in the absence of other strong risk factors. However, it is established that deficiency in DNA repair mechanisms or higher mutagen sensitivity, as assessed by the induction of chromatid breaks, may play an important role in the development of melanoma *(2,3)*.

The absence of association between DRC and melanoma risk observed in the study by Landi et al. may be caused by a lack of sensitivity in the host cell reactivation assay. This assay measures DRC in lymphocytes that have not been exposed to the genotoxic stimulus (UV radiation). Indeed, UV-induced DNA

damage triggers the induction of photoprotective responses, such as an increased DRC *(4)*.

Alternatively, in the population selected by Landi et al., this absence of association may result from an age effect among case patients and control subjects or from differences in the distribution of individual DRC values between case patients and control subjects.

Inherited susceptibility factors are likely to be more manifest at an earlier age *(5)*. When we analyzed data from a cutaneous melanomas registry for the region of Burgundy, France, we found that host susceptibility factors, such as eye color, which is classically associated with melanoma risk, actually appeared to be risk factors for the occurrence of melanoma before 50 years of age *(6)*. Furthermore, to explore the relationship between inherited susceptibility to UV radiation and the risk of melanoma, we measured the apoptosis triggered in peripheral blood lymphocytes by a low dose of UVB radiation and considered the following two age groups of patients with cutaneous melanoma of the SSM (superficial spreading melanoma) type and of healthy control subjects: 18–39 years old and 60–69 years old. We observed that UVB induced more apoptosis in lymphocytes from patients with melanoma than in lymphocytes from control subjects ($P<.001$). This difference is highly statistically significant in the younger group, but there is no difference in the older group (Fig. 1, unpublished results).

In the study by Landi et al., among control subjects, as expected, DRC decreases with increasing age, but DRC does not decrease accordingly among case patients or control subjects with dysplastic nevi or high nevus counts, where DRC may even increase with age. Of note, case patients are slightly older than control subjects (48.0 years versus 44.6 years). Analysis of the risk of melanoma by DRC, taking as a cutoff value the median value of DRC in control subjects, may also mask differences in the distribution of individual DRC values between case patients and control subjects. Therefore, it would be of interest to compare distributions of DRC in case patients and control subjects and to analyze the association of melanoma with DRC in patients younger than 40–50 years by the use of a lower cutoff value. The current analysis does not exclude the possibility that patients with melanoma may actually suffer from some kind of susceptibility to UV radiation at the cellular level.

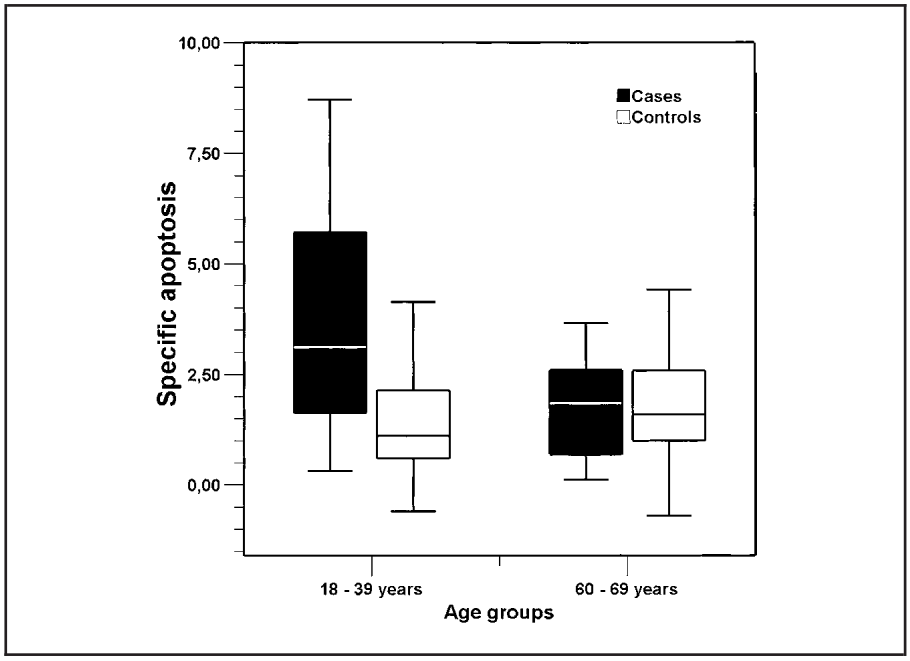

Fig. 1. Apoptosis (detected by TUNEL [terminal deoxynucleotidetransferase-mediated deoxyuridine 5′-triphosphate nick end labeling] procedure) induced by 50 J/m^2 UVB irradiation in peripheral blood lymphocytes from patients with cutaneous melanoma (superficial spreading melanoma [SSM]) and healthy controls. Specific apoptosis was calculated as $Ap_{SP} = (Ap_{UV} - Ap_{CT})/Ap_{CT,}$ where Ap_{UV} is the percentage of apoptotic cells in UVB-irradiated samples and Ap_{CT} is the spontaneous apoptosis in nonirradiated samples. **Boxplots** represent interquartile ranges and extreme values, and **horizontal bar** denotes the median.

RÉMY PEDEUX
MATHIEU BONIOL
PHILIPPE AUTIER
JEAN-FRANÇOIS DORÉ

REFERENCES

(1) Landi MT, Baccarelli A, Tarone RE, Pesatori A, Tucker MA, Hedayati M, et al. DNA repair, dysplastic nevi, and sunlight sensitivity in the development of cutaneous malignant melanoma. J Natl Cancer Inst 2002;94:94–101.

(2) Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. Arch Dermatol 1994;130:1018–21.

(3) Wu X, Hsu TC, Spitz MR. Mutagen sensitivity exhibits a dose-response relationship in case–control studies. Cancer Epidemiol Biomarkers Prev 1996;5:577–8.

(4) Eller MS, Maeda T, Magnoni C, Atwal D, Gilchrest BA. Enhancement of DNA repair in human skin cells by thymidine dinucleotides: evidence for a p53-mediated mammalian SOS response. Proc Natl Acad Sci U S A 1997;94:12627–32.

(5) Wei Q, Cheng L, Amos CI, Wang LE, Guo Z, Hong WK, et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst 2000;92:1764–72.

(6) Boniol M, Sallin J, Dore JF. Time trends of cutaneous melanoma in Queensland, Australia and Central Europe. Cancer 2002;94:1902–3.

NOTES

Affiliation of authors: R. Pedeux, M. Boniol, J.-F. Doré, Institut National de la Santé et de la Recherche Médicale, Unité 453, Lyon, France; P. Autier, Centre de Recherche Public de la Santé, Luxemburg, Luxemburg.

Present address and correspondence to: Rémy Pedeux, Ph.D., Laboratory of Human Carcinogenesis, National Cancer Institute, National Institutes of Health, 37 Convent Dr., Bldg. 37, Rm. 2C26, Bethesda, MD 20892 (e-mail: pedeuxr@mail.nih.gov).

RESPONSE

We thank Pedeux et al. for their interesting comments. It is true that the host cell reactivation assay is based on lymphocytes that are not exposed to UV. Indeed, this fact is a strength of the assay *(1)* because it allows measurement of constitutional DNA repair capacity (DRC) that is independent of secondary damage that might be caused by UV exposure to the host cells. UV may induce DRC *(2)* and tanning *(3)* in cultured skin cells, but the effects of sunlight exposure *in vivo* are not known (and are not amenable to measurement in an epidemiologic study). In our article we referenced a small investigation *(4)* con-

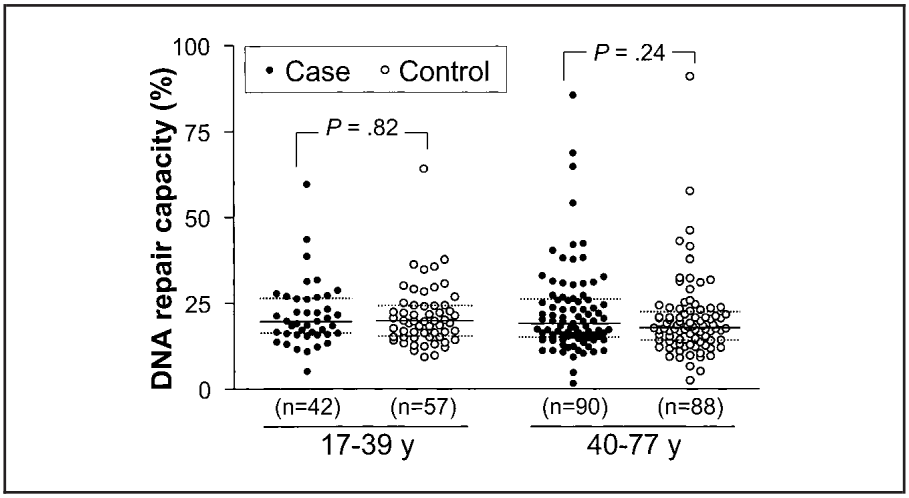

Fig. 1. DNA repair capacity (DRC) by age groups in case patients with cutaneous malignant melanoma and control subjects. DRC was measured in peripheral blood lymphocytes with the host cell reactivation assay and was calculated as the percentage of residual chloramphenicol acetyltransferase gene expression after the repair of 254 nm (350 J/m^2) UV radiation-damaged plasmid DNA divided by that in undamaged plasmid DNA (100%). The two-sided Wilcoxon (Mann–Whitney) rank-sum test was used for group comparison. **Solid** and **dotted lines** indicate medians and interquartile (25th–75th centile) ranges, respectively.

ducted in skin biopsy specimens taken immediately after UV irradiation from melanoma case patients and control subjects. Similar to our results, no overall association between DRC and melanoma risk was found. In our study, recreational sun exposure was marginally associated with DRC among case patients (Table 2 in the original manuscript) but did not differ statistically significantly between case patients and control subjects. In addition, there was no statistical interaction between DRC and lifetime recreational sun exposure in their association with melanoma risk. For these reasons, we did not control for sun exposure in the analyses reported. However, all the results were practically identical when the models were adjusted for lifetime recreational sun exposure (between 11:00 AM and 3:00 PM), for occupational sun exposure, or for recent (up to 5 months before the study) sun exposure. Thus, although we cannot directly measure the effects of UV-induced photoprotective responses, we think it is unlikely that our results are distorted by differential UV-dependent induction of DRC between case patients and control subjects.

As for the second hypothesis raised in the letter, a slight decrease in DRC with age in healthy subjects and an interaction between DRC and age in their association with skin cancer risk have been described *(5,6).* Our case–control study was frequency matched by decade of age, and all analyses reported in the manuscript were adjusted for age. We have reproduced the analysis presented for apoptosis and report the distribution of DRC by case–control status and by age (Fig. 1). There is no evidence of effect modification by age. Similarly, there was no difference in DRC when we used the median age (46 years) as a cutoff value for the analysis. Although the authors' results on apoptosis are intriguing, the possibility of false-positive findings is increased by *post hoc* subgroup analyses; thus, such analyses must be interpreted with caution. In this regard, the apoptosis results for ages 40–59 years would be required to fully interpret the hypothesized effect modification by age for apoptosis.

MARIA TERESA LANDI
ANDREA BACCARELLI
ANGELA C. PESATORI
MOHAMMAD HEDAYATI
LAWRENCE GROSSMAN
MARGARET A. TUCKER
ROBERT E. TARONE

REFERENCES

(1) Berwick M, Vineis P. Markers of DNA repair and susceptibility to cancer in humans: an epidemiologic review. J Natl Cancer Inst 2000; 92:874–97.

(2) Eller MS, Maeda T, Magnoni C, Atwal D, Gilchrest BA. Enhancement of DNA repair in human skin cells by thymidine dinucleotides: evidence for a p53-mediated mammalian SOS response. Proc Natl Acad Sci U S A 1997;94: 12627–32.

(3) Eller MS, Gilchrest BA. Tanning as part of the eukaryotic SOS response. Pigment Cell Res 2000;13 Suppl 8:94–7.

(4) Xu G, Snellman E, Bykov VJ, Jansen CT, Hemminki K. Cutaneous melanoma patients have normal repair kinetics of ultraviolet-induced DNA repair in skin *in situ.* J Invest Dermatol 2000;114:628–31.

(5) Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L. DNA repair and aging in basal cell carcinoma: a molecular epidemiology study. Proc Natl Acad Sci U S A 1993; 90:1614–8.

(6) Goukassian D, Gad F, Yaar M, Eller MS, Nehal US, Gilchrest BA. Mechanisms and implications of the age-associated decrease in DNA repair capacity. FASEB J 2000;14: 1325–34.

NOTES

Affiliations of authors: M. T. Landi, M. A. Tucker, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; A. Baccarelli, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, and Epidemiology Research Center, University of Milan, Italy; A. Pesatori, Epidemiology Research Center, University of Milan; M. Hedayati, L. Grossman, Department of Biochemistry, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD; R. E. Tarone, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute.

Correspondence to: Maria Teresa Landi, M.D., Ph.D., Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd. EPS 7114, Bethesda, MD 20892–7236 (e-mail: landim@mail.nih.gov).